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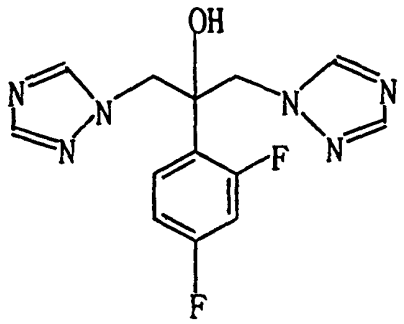
(54) Title: PROCESS FOR MANUFACTURING FLUCONAZOLE

(57) Abstract

The invention herein relates to a process for the manufacture of fluconazole, or more particularly, to the process for the manufacture of fluconazole of Formula (1) having superior antifungal activity with a high yield and purity, and its pharmaceutically acceptable salt or hydrate, wherein one-pot reaction is utilized under the mild reaction condition and short reaction time by means of using three compounds expressed by formulae (2, 3 and 4), respectively, in the presence of a base.



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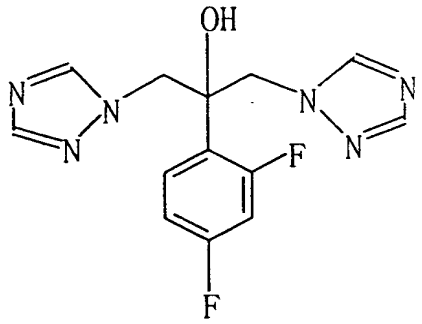
Process for Manufacturing Fluconazole

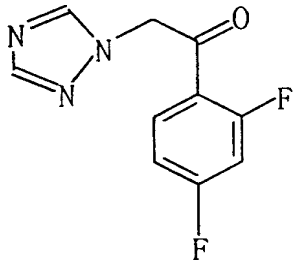
Field of the Invention

The invention herein relates to a process for the manufacture of fluconazole, or more particularly, to the process for the manufacture of fluconazole of Formula 1 having superior antifungal activity with a high yield and purity, and its pharmaceutically acceptable salt or hydrate, wherein one-pot reaction is utilized under a mild reaction condition and short reaction time by means of using three compounds expressed by the following formula 2, 3, and 4, respectively, in the presence of a base.

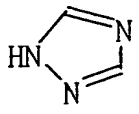
Formula 1



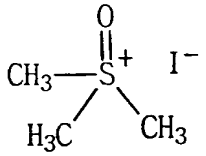
Formula 2



Formula 3



Formula 4



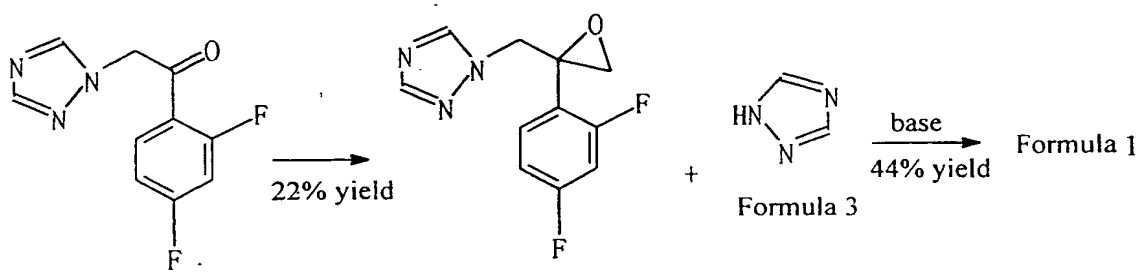
Background of the Invention

Fluconazole, expressed by Formula 1, was developed in 1982 [U.K. Patent Application No. 2078719 (1982); Korean Patent Application No. 82-2493] and has been widely used as effective antifungal agents in the clinical field.

U. K. Patent Application No. 2270521 (1993) discloses a method of synthesizing fluconazole monohydrate from fluconazole anhydrous. According to the U.K. patent, the water content of fluconazole anhydrous was 0.1% while that of fluconazole monohydrate was 5.6%.

Korean Patent Application No. 82-2493. discloses a method of manufacturing fluconazole of Formula 1 based on the process as shown in the following Scheme 1.

Scheme 1

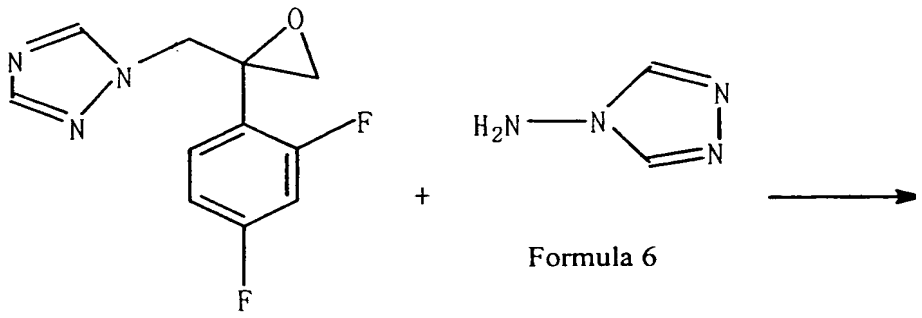


Formula 2 Formula 5

From the above reaction, when the compound of Formula 5 is synthesized from the compound of Formula 2, the production yield (22%) therefrom is quite low. When the compound of Formula 5 is reacted with the compound of Formula 3 in order to synthesize the compound of Formula 1, the production yield therefrom is 44%, and the total production yield (9.6%) is extremely low.

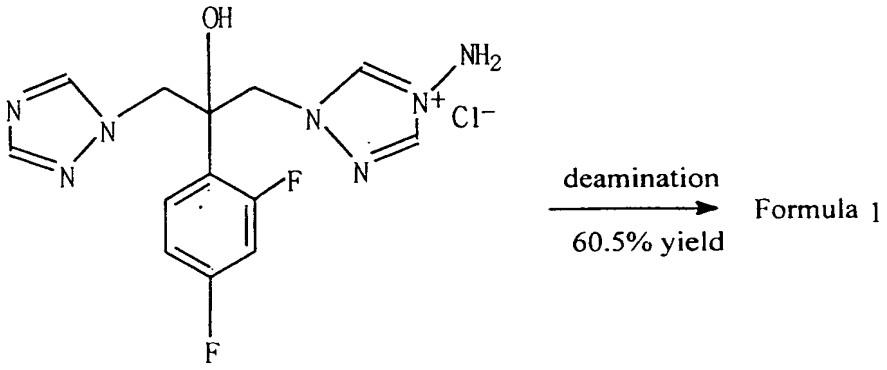
Another method disclosed in the Korea Patent Application No. 94-6165 is to synthesize fluconazole expressed by Formula 1 based on the manufacturing process as shown in the following scheme 2.

Scheme 2



Formula 5

Formula 6



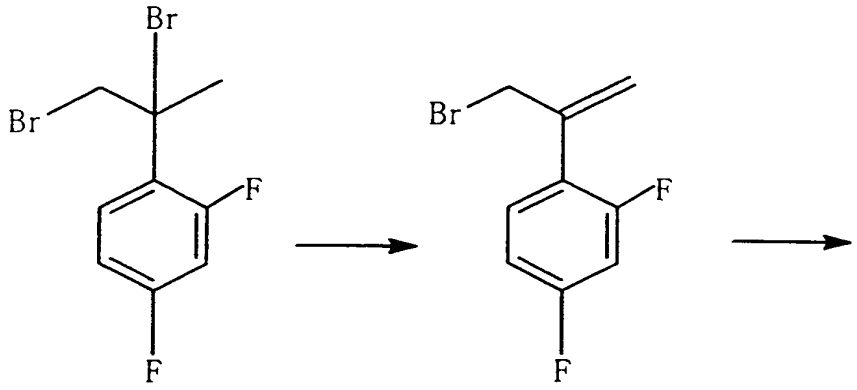
Formula 7

Formula 1

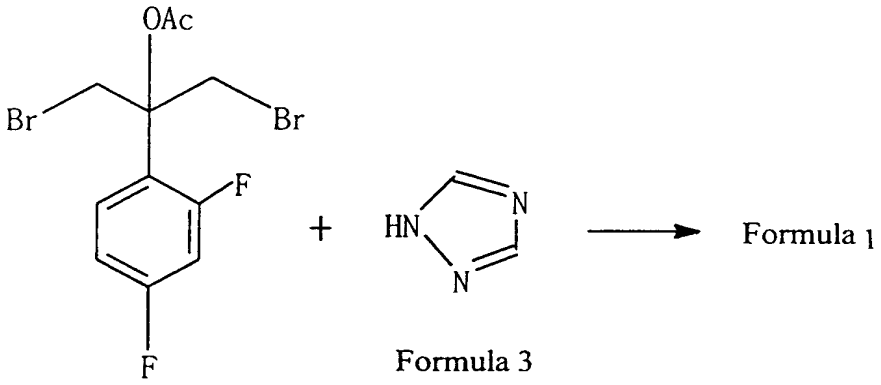
According to Scheme 2, the compound of Formula 5 is reacted with the compound of Formula 6, followed by an intermediate expressed by Formula 7, and fluconazole is synthesized having its production yield of 60.5%. However, when the compound of Formula 5, the starting material, is used, the production yield from the compound expressed by Formula 2 is not more than 22% (Korea Patent Application No. 82-2493). Thus, the actual total yield based on this method is as low as 13.3%. In order to de-aminated the compound expressed by Formula 7, so generated as a reaction intermediate, a corrosive acid with toxicity and sodium nitrite must be employed. In addition, the de-amination under such conditions must be performed at an extremely low temperature, and if the adjustment to such temperature fails, there is a risk of explosion. Therefore, Scheme 2 does not seem to be adequate for the large-scale industrial production.

Meanwhile, International Unexamined Patent No. 95-7895 discloses a method of synthesizing a compound expressed by Formula 1, as shown in the following scheme 3.

Scheme 3



Formula 8 Formula 9



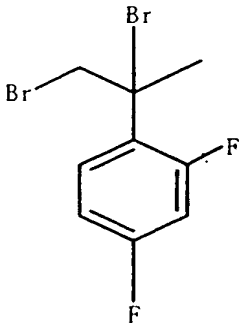
Formula 3

Formula 10

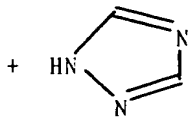
The total yield based on the scheme 3 also proves not to be in a satisfactory level as it is only 27%. Besides, when the compound of Formula 9 is prepared, the reaction must be performed at a high temperature (140-160℃), and bromination intended for manufacturing the compound of Formula 10 is extremely dangerous as a radical reaction, and some reagents used for this reaction is quite toxic, thus making it difficult to apply the scheme 3 to the industrial purpose.

Further, International Unexamined Patent No. 96-20181 discloses a method of synthesizing a compound expressed by Formula 1, as shown in the following scheme 4.

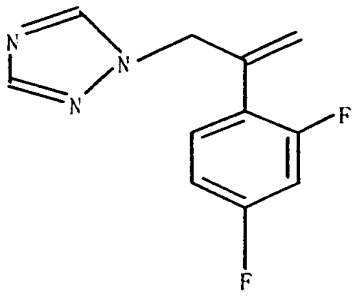
Scheme 4



Formula 8

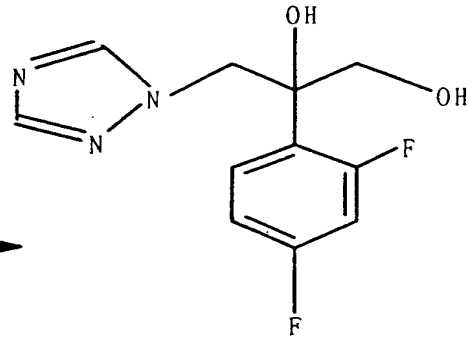


Formula 3



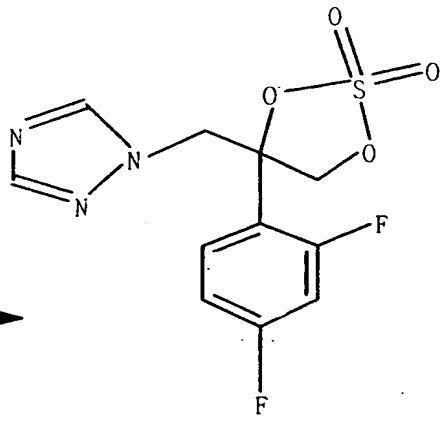
Formula 11

KMnO 4

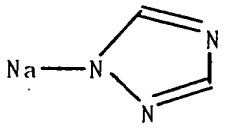


Formula 12

SO_2Cl_2



Formula 13



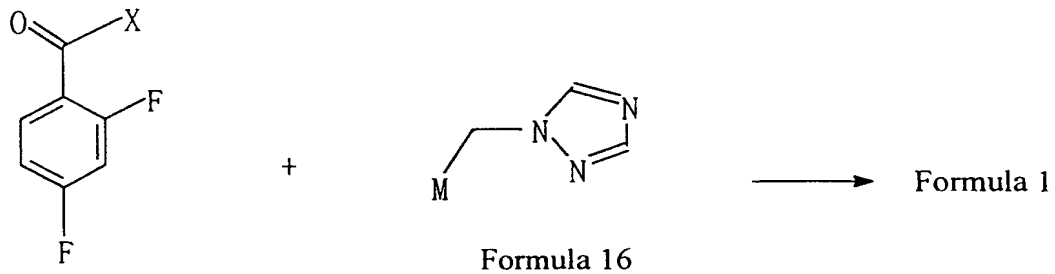
Formula 14

→ Formula 1

The total yield based on the scheme 4 also proves to be extremely low as it is only 14.8%. In addition, KMnO4, an oxidant used for the manufacture of the compound of Formula 12, is quite dangerous owing to its vehement and exothermic reaction, and the removal of MnO2 generated as a by-product after the oxidation is not easy. Further, SO2Cl2 used for the synthesis of a compound expressed by Formula 13 at the final step is quite toxic and explosive. In this respect, it can be said that the conventional manufacturing process is not adequate for the industrial process.

Unlike the conventional prior arts, the Spanish Patent Nos. 8604939, 8605753 and 2049663 disclose one-step manufacturing process of synthesizing a compound expressed by Formula 1, as shown in the following scheme 5.

Scheme 5



Formula 15

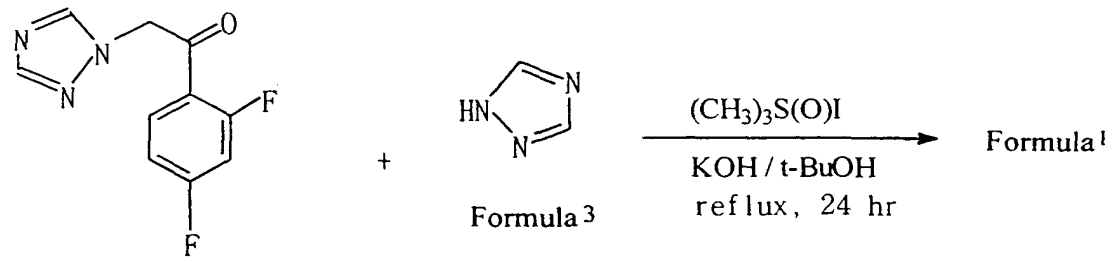
Formula 16

where X is OCH3, OCH2CH3 or Cl; M is MgBr or Li.

According to the one-step manufacturing process based on the scheme 5, the target compound was synthesized with a relatively high yield (45-85%). Nevertheless, 1-(halomethyl)-1,2,4-triazole used for the synthesis of the compound of Formula 16 is an expensive reagent, the synthesis of such compound is not easy, and its yield is quite low. Since the Grignard reagent or the reagent containing lithium used for this reaction has an explosively high reactivity and is very sensitive to water and air, the reaction must be performed in the anhydrous condition. Hence, the application of the scheme 5 is extremely difficult in the commercial production.

Meanwhile, Bauer et al. at Illinois University synthesized a compound expressed by Formula 1, as shown in the following scheme 6 (J. Heterocyclic Chem., 30. 1405, 1993).

Scheme 6



Formula 2 + Formula 3 → Formula 1

According to the manufacturing process based on the scheme 6, Bauer et al. reported that the production yield of a compound expressed by Formula 1 was 38% when the mixture of two compounds of Formula 2 and 3 were refluxed for 24 hours in the presence of trimethylsulfoxonium iodide (Formula 4) and potassium hydroxide in t-butanol. Unlike the conventional prior arts, the above manufacturing process comprises one-step reaction which is performed under a mild condition without using industrially non-applicable reagents. With the production yield of 38%, the manufacturing process based on the scheme 6 succeeds in overcoming some of the problems of the conventional methods (e.g., low yield and reaction conditions) to some extent. Nonetheless, the scheme 6 has a disadvantage in that since the reactants are subjected to heterogeneous reaction, the reaction time becomes extended up to 24 hours, and the separation and purification of the by-products are not easily made available. In particular, for the purposes of the separation and purification of the compound expressed by Formula 1, the target product, the silica gel column is not suitable for the industrial production. As a result of performing the test based on the method as described in the above referential example of said invention and analyzing the final product by HPLC (TSKgel, ODS-80TM (4.5x150mm) column), the relative area ratio of fluconazole (RT 4.65) within the reacting solution was 23% while the majority of by-products occupied 73% in the reacting solution. In this regard, it is understood that many of the by-products were generated under such reaction condition.

As mentioned above, the conventional methods intended for synthesizing fluconazole of Formula 1 have several commonly recognized disadvantages in that a) some reagents used for the reaction are quite dangerous or complicated, b) in particular, where the reactants are not homogeneously dissolved in a solvent, a large amount of by-products during the reaction results with a lower yield, and c) the process of separating and purifying the target compound is not easily available so that its industrial application has been proven difficult. Therefore, there is an urgent need for a novel process in which the compound of Formula 1 may be easily prepared with a high yield.

SUMMARY OF THE INVENTION

To overcome the above mentioned shortcomings, the inventor et al. have conducted intensive studies covering the method of synthesizing fluconazole expressed by Formula 1 in an easy manner with a high yield and purity. Therefore, the invention herein has been devised using water or a co-solvent consisting of water and an organic solvent, so as to ensure the homogeneous reaction where reagents are completely dissolved under a mild condition and with easily handled reagents.

Therefore, the objective of said invention is to provide a process of manufacturing fluconazole expressed by Formula 1 in an easy manner with a high yield and purity via the reaction in which the completely dissolved reagents are in homogeneous state.

Brief Description of the Drawings

Fig. 1a shows the results of the HPLC analysis of the reaction solution prior to the addition of the compound expressed by Formula 3 from the conventional process of manufacturing fluconazole based upon in-situ reaction.

Fig. 1b shows the results of the HPLC analysis of the reaction solution which has been in a reaction for one hour with the addition of the compound expressed by Formula 3 from the conventional process of manufacturing fluconazole based upon in-situ reaction.

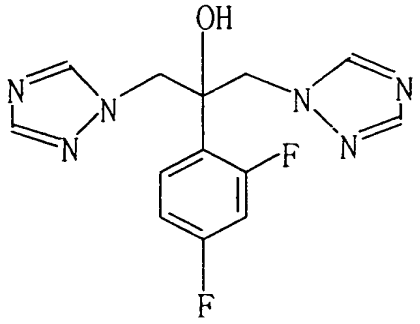
Fig. 2 shows the results of the HPLC analysis of the one-pot reaction of said invention.

Fig. 3 show the results of the HPLC analysis of the reaction solution according to the referential example (J. Heterocyclic Chem., 30, 1405, 1993).

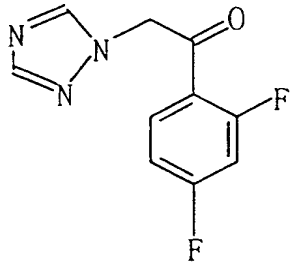
Detailed Description of Preferred Embodiments

The invention herein relates to a process of manufacturing fluconazole expressed by Formula 1 using two compounds of Formula 3 and 4 respectively, and the compound of Formula 2 as a starting material, wherein two compounds of the Formula 3 and 4 are added to the compound of Formula 2 for one-pot reaction. The reaction is carried out by selecting water, or an organic solvent which may be mixed with water and a water-mixed co-solvent.

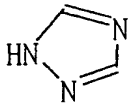
Formula 1



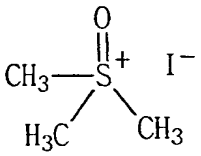
Formula 2



Formula 3



Formula 4



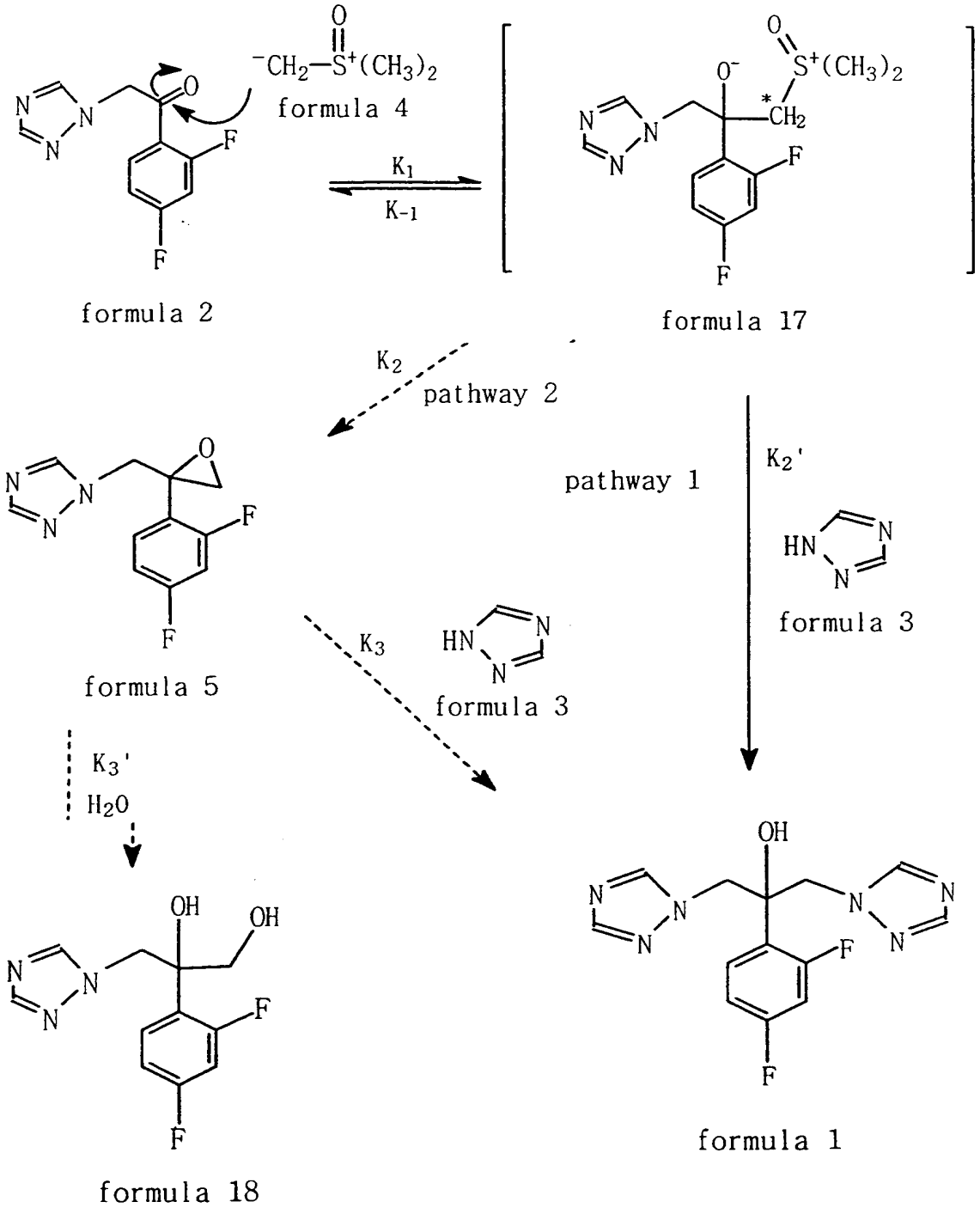
The invention is explained in more detail as set forth hereunder.

According to said invention, the reaction is carried out by selecting water, or an organic solvent which may be mixed with water and a water-mixed co-solvent, thus allowing the reaction reagents to be completely dissolved. Under the above reaction condition, said invention has several advantages in that a) compared with the reaction performed in the presence of a conventional organic solvent such as t-butanol (J. Heterocyclic Chem., 30, 1405, 1993), its production yield increases from 38% to 70%

or more, b) reaction time is shortened to one or two hours from 24 hours, c) reduction in the by-products in the reaction may facilitate separation and purification of the target product.

Further, the reactants used during the process of manufacturing fluconazole according to said invention is the same as that used in the Korea Patent Application No. 82-2493. However, said invention is entirely different from the later in terms of order and methods in adding the reactants. The invention herein generates new reaction conditions within the system, and as a result, it was confirmed that some unexpected effects such as reaction yield, etc. had occurred. Since said invention is different from the conventional methods in terms of the reaction method, it is assumed that each of the different reaction mechanism may contribute much to the remarkable synergic effect in the production yield. The manufacturing process under said invention (one-pot reaction), and in situ reaction mechanism based on the Korea Patent Application No. 82-2493 may be illustrated in the following scheme 7.

Scheme 7


formula 4
K1
K-1
formula 2
formula 17
K2
pathway 2
pathway 1
K2'
formula 3
K3
formula 3
formula 5
K3'
H2O
formula 1
formula 18

As shown in Scheme 7, both inventions employ the compounds expressed by Formula 2, 3 and 4 respectively, and as such, two pathways in their reaction mechanism may be predicted.

The manufacturing process under the Korea Patent Application No. 82-2493 is characterized in that epoxide expressed by Formula 5, so generated as an intermediate, is separately isolated, and then the above compound is reacted with the compound of Formula 3 to synthesize fluconazole of Formula 1. This process corresponds to the mechanism where the compound of Formula 3 is subjected to in-situ reaction after the starting material is completely converted to the intermediate compound. Compared to the conventional process of separating the intermediate, the in-situ reaction has been reported to have an improved production yield. The in-situ reaction is actually carried out in such a manner that the first-step process is internally complete without the second-step reaction or intermediate-separation process. Immediately thereafter, the second-step process is performed. Such process appears be a first-step process, but it includes second-step process in terms of reaction mechanism.

In contrast, the manufacturing process of the invention is basically different from that of the in-situ reaction since its first-step reaction is carried out with the addition of reaction materials at the initial stage irrespective of any generation of intermediates (Formula 5 and 17).

To ascertain the difference of the production yields between the conventional in-situ reaction and the reaction mechanism under the invention herein, the following tests have been performed.

First, it was confirmed that in the conventional method, two compounds expressed by Formula 2 and 4 were reacted in the presence of a base. As a result of the HPLC analysis, the compound of Formula 2, the starting material, completely disappeared (refer to attached Fig. 1a). With the in-situ addition of the compound of Formula 3, the mixture was again reacted for 1 hour. The reaction solution was analyzed using the HPLC. The results of the analysis therefrom are shown in Fig. 1b. Then, three compounds with the Formula 2, 3 and 4 were subjected to the one-pot reaction, and the reaction solution was analyzed by HPLC. The results of the analysis therefrom are revealed in Fig. 2.

1. Conventional method (in-situ reaction)
   a) Reaction solution prior to addition of the compound of Formula 3:
      RT 1.3 (17%, a compound of Formula 4),
      RT 3.89 (9.5%, a compound of Formula 18),
      RT 6.28 (6%, unknown compound),
      RT 10.57 (7.3%, unknown compound),
      RT 11.52 (56.5%, a compound of Formula 5),
      Others (3.7%)

b) Reaction solution one hour after addition of the compound of Formula 3:

RT 1.4 (15%, compound of Formula 4),
RT 3.02 (4%, regio-isomer of fluconazole),
RT 3.91 (22%, compound of Formula 18),
RT 4.56 (17%, compound of Formula 1),
RT 6.32 (7.3%, unknown compound),
RT 10.62 (20%, unknown compound),
Others (8%)

2. Manufacturing process of said invention (one-pot reaction):

RT 1.4 (18.7%, compound of Formula 4),
RT 3.02 (14%, regio-isomer of fluconazole),
RT 3.91 (4.0%, compound of Formula 18),
RT 4.56 (52%, compound of Formula 1),
RT 6.32 (7.3%, unknown compound),
Others (11.3%)

As shown in the HPLC analysis results, the in-situ reaction had high production rates of by-products expressed by Formula 18 and unknown compounds instead of fluconazole, and the generation yield of fluconazole based on quantitative analysis was 33.8%. In contrast, according to the reaction as described in the examples of said invention, its main product is fluconazole of Formula 1, the target compound, and the production yield of fluconazole based on quantitative analysis was 88%.

The significant difference of the production yields lies in the fact that unlike Korea Patent Application No. 82-2493, the reaction mechanism based said invention does not involve a compound expressed by Formula 5.

The reaction mechanism based of said invention is explained in more detailed as set forth hereunder.

In general, the reaction between sulfoxonium ylide and carbonyl group is a reversible reaction, and its reaction rate has been reported to be very fast. In contrast, the nucleophilic substitution between the compound of Formula 17 and nucleophiles is an irreversible reaction, and its reaction rate has been reported to be very slow as compared to that in the first-step reaction. Therefore, the rate determining step of this reaction is a nucleophilic substitution step. If the compound of Formula 17 is stable enough to be present during the reaction time with other nucleophiles, the relative ratio of the final product is determined by the nucleophilic substitution rate.

In short, the relative production ratio of a product from the rate determining step is determined by the reaction rate. Since the reaction rate via pathway 1 is relatively faster than that of the pathway 2, the compound of Formula 1 is mainly generated via pathway 1.

The main reaction mechanism according to said invention is assumed to be based on the nucleophilic substitution between the two compounds expressed by Formula 17 and 3, respectively while the mechanism via the compound of Formula 5 is assumed to be an additional reaction.

Further, the yields under the process as set forth in Bauer et al. [J. Heterocyclic Chem., 30. 1405, 1993] are relatively lower than that of the process under said invention. Bauer et al. uses t-BuOH as a solvent, and the compound of Formula 3 used in the reaction is quite soluble in water but not so in t-BuOH. Consequently, the concentration of the compound of Formula 3 that may enter into the reaction process is rather low. It is rather improbable that the compound of Formula 17 be converted into the compound of Formula 1 via the direct reaction with the compound of Formula 3. It is more likely that the compound of Formula 17 is converted into the compound of Formula 1 via the compound of Formula 5 which is relatively more stable than the compound of Formula 17. However, a decrease in the compounds entering the pathway 1, the most efficient pathway, leads to a general reduction in yield.

In other words, in order to activate the pathway 1, a solvent which will sufficiently dissolve the compound of Formula 3 is needed. Under said invention, the homogeneous reaction system, in which the compound of Formula 3 is completely dissolved, is used.

According to said invention, water or a co-solvent consisting of water and organic solvent is used as a reaction solvent so as to effectuate the homogeneous reaction. Accordingly, an organic solvent, which may be mixed with water, is employed. For example, it is preferred to select from acetonitrile, dimethylformamide, dimethyl sulfoxide, and one or more lower alcohols having carbon number of 1-4.

In case of using these organic solvents and a water-mixed co-solvent, nearly similar or somewhat higher production yield may be obtained as compared to the situation in which water is used as a single solvent while the reaction temperature is slightly lowered, and the compound expressed by Formula 2 may be easily dissolved. Further, as for the co-solvent consisting of water and organic solvent, it is preferred to maintain its volume ratio in the range of 1:0.1-1:10, more particularly in the volume ratio of 1:0.1 - 1:1.

As for the manufacturing process under said invention, it is preferable to use 1 g of the compound of Formula 2 in 5 - 10 ml and the reaction temperature in the range of 50℃ and the reflux temperature.

As for the reagent used for the manufacturing process of said invention, it is preferred that each of two compounds expressed by Formula 3 and 4 respectively, be used in the equivalent ratio of 1 to 2, in proportion to the compound expressed by Formula 2. According to the manufacturing process of said invention, a common type of base may be used. There are, for example, potassium hydroxide and sodium hydroxide as a base. It is preferred that its amount be in the equivalent ratio of 2 to 4, in proportion

to the compound of Formula 2.

Through the above process, fluconazole is prepared in the form of monohydrate. Further, the invention herein includes a process of manufacturing fluconazole expressed by Formula 1, its pharmaceutically acceptable salt or hydrate.

The materials commonly available may be applicable in the manufacture of the pharmaceutically acceptable salt of fluconazole, and its manufacture may be easily made available by the common method.

Further, no case of converting fluconazole anhydrous to fluconazole monohydrate, so prepared by the above manufacturing process, had been reported, but one case of converting fluconazole anhydrous to fluconazole monohydrate was disclosed in the U.K. Patent Application No. 270521 (1993).

According to said invention, fluconazole monohydrate is dissolved in the alcohol solvent at a hot temperature (40℃ to reflux temperature) and cooled at below 5℃. Then fluconazole anhydrous was prepared either by precipitating and filtering fluconazole anhydrous or by removing the solvent under vacuum.

The invention herein will be more fully understood by the following examples which illustrate the invention but are not to be considered limitation to the scope of the invention.

Referential example: based on the reference as described by J. Heterocyclic Chem., 30, 1405, 1993

A mixture of 2',4'-difluoro-2-(1H-1,2,4-triazol-1-yl)acetophenone (5.0g, 22.4mmol), trimethylsulfoxonium iodide (6.0g, 26.88mmol), 1,2,4-triazole (1.86g, 26.88mmol), and potassium hydroxide (3.55g, 53.76mmol) were refluxed for 24 hours in t-butanol (40ml). After the reaction solution was cooled to room temperature, water was added to the reaction solution up to 70ml and stirred until all materials were completely dissolved. 1ml of the reaction solution was collected and diluted to 100ml. Then the solution was analyzed by HPLC (TSK gel, ODS-80TM (4.5x150mm) column), and its results are revealed in the attached Fig. 3. The general method of purifying and separating fluconazole from the reaction solution has proven to be difficult owing to the generation of by-products. Such separation process was performed on silica gel column, and as a result, its yield was similar to that of the method in above literature (38%).

HPLC analysis: RT 1.46 (10.79%, trimethylsulfoxonium iodide), RT 4.01 (10.76%, 2-(2',4'-difluoropenyl)-2,3-dihydroxypropyl-1H-1,2,4-triazole), RT 4.67 (23.4%, fluconazole), RT 2.66 (4.09%, unknown compound), RT 3.06 (8.31%, unknown compound), RT 6.46 (12.98%, unknown compound), and others (17 by-products)

Example 1: Preparation of fluconazole monohydrate

2',4'-Difluoro-2-(1H-1,2,4-triazol-1-yl)acetophenone (5.0g, 22.4mmol), trimethylsulfoxonium iodide (6.0g, 26.88mmol), 1,2,4-triazole (1.86g, 26.88mmol), and potassium hydroxide (3.55g, 53.76mmol) were refluxed for 1 hour in the presence of a co-solvent consisting of potassium hydroxide solution and isopropanol (20ml) dissolved in distilled water (20ml). Isopropanol from the reaction solution was evaporated and neutralized with 10% HCl solution. This aqueous solution was extracted with methylene chloride (100ml) and washed with saturated sodium bicarbonate solution (50ml), Then this methylene chloride layer was extracted with 5% HCl solution (50ml). The aqueous solution, so extracted, was washed with ethyl acetate (50ml), and with the addition of activated carbon (1.0g), the reaction solution was stirred for 30 minutes and filtered. The filtrate was cooled at below 5℃, neutralized with ammonia water and stirred for 1 hour. The precipitate was filtered and washed with water. A white solid, so formed by filtering, was dried for 5 hours under vacuum.

As a result, a white solid compound, so prepared, was confirmed to be fluconazole monohydrate (5.52g; yield 76%), and it coincided with those materials prepared by the Korean Patent Application No. 82-2493, and U.K. Patent Application No. 2270521 (1993) in terms of IR (KBr), 1H NMR and water content (5.6%).

1H NMR (DMSO-d6, 300MHz) : δ 8.3 (2H, s), 7.8 (2H, s), 7.1-7.24 (2H, m), 6.85 (1H, m), 6.35 (1H, s), 4.55 (2H, d), 4.73 (2H, d)

M.P.: 138-139℃

Example 2: Preparation of fluconazole monohydrate

A mixture of 2',4'-difluoro-2-(1H-1,2,4-triazol-1-yl)acetophenone (5.0g, 22.4mmol), trimethylsulfoxonium iodide (6.0g, 26.88mmol), 1,2,4-triazole (1.86g, 26.88mmol) and sodium hydroxide (2.2g, 53.76mmol) were refluxed for 1 hour in the presence of a co-solvent consisting of sodium hydroxide solution and isopropanol (20ml) dissolved in distilled water (20ml). Then the reaction was carried out in the same manner as described in the example 1.

As a result, a white solid compound, so prepared, was confirmed to be fluconazole monohydrate (5.37g; yield 74%), and it coincided with those materials prepared by the Korean Patent Application No. 82-2493, and U.K. Patent Application No. 2270521 (1993) in terms of IR (KBr), 1H NMR (DMSO-d6) and water content (5.6%).

Example 3: Preparation of fluconazole monohydrate

2',4'-Difluoro-2-(1H-1,2,4-triazol-1-yl)acetophenone (5.0g, 22.4mmol), trimethylsulfoxonium iodide (6.0g, 26.88mmol), 1,2,4-triazole (1.86g, 26.88mmol), and potassium hydroxide (3.55g, 53.76mmol) were refluxed for 1 hour in the presence of a co-solvent consisting of potassium hydroxide solution and each organic solvent (20ml) dissolved in distilled water (20ml), as shown in the following table 1. Then the reaction was carried out in the same manner as described in the example 1.

As a result, a white solid compound, so prepared, was confirmed to be fluconazole monohydrate, and it coincided with those materials prepared by the Korean Patent Application No. 82-2493, and U.K. Patent Application No. 2270521 (1993) in terms of IR (KBr), 1H NMR (DMSO-d6) and water content (5.6%).

Table 1.

Organic solvent	Methanol	Dimethylform amide	Acetonitrile
Yield	5.3g(73%)	5.16g(71%)	5.4g(74%)

Example 4: Preparation of fluconazole monohydrate

2',4'-Difluoro-2-(1H-1,2,4-triazol-1-yl)acetophenone (5.0g, 22.4mmol), trimethylsulfoxonium iodide (6.0g, 26.88mmol), 1,2,4-triazole (1.86g, 26.88mmol), and potassium hydroxide (3.55g, 53.76mmol) were refluxed for 1 hour in the presence of potassium hydroxide solution dissolved in distilled water (40ml). Then the reaction was carried out in the same manner as described in the example 1.

As a result, a white solid compound, so prepared, was confirmed to be fluconazole monohydrate (5.4g, yield: 74.5%), and it coincided with those materials prepared by the Korean Patent Application No. 82-2493, and U.K. Patent Application No. 2270521 (1993) in terms of IR (KBr), 1H NMR (DMSO-d6) and water content (5.6%).

Example 5: Preparation of fluconazole monohydrate

A mixture of 2',4'-difluoro-2-(1H-1,2,4-triazol-1-yl)acetophenone (5.0g,

22.4mmol), trimethylsulfoxonium iodide (6.0g, 26.88mmol), 1,2,4-triazole (1.86g, 26.88mmol) and potassium hydroxide (3.55g, 53.76mmol) were stirred at each temperature (table 2) for 2 hours in the presence of a co-solvent consisting of potassium hydroxide solution and isopropanol (20ml) dissolved in distilled water (20ml). Then the reaction was carried out in the same manner as described in the example 1.

As a result, a white solid compound, so prepared, was confirmed to be fluconazole monohydrate, and it coincided with those materials prepared by the Korean Patent Application No. 82-2493, and U.K. Patent Application No. 2270521 (1993) in terms of IR (KBr), 1H NMR (DMSO-d6) and water content (5.6%).

Table 2.

Reaction temp.	60℃	65℃	70℃	75℃
Yield	5.3g(73%)	5.45g(75%)	5.15g(71%)	5.15g(71%)

Example 6: Preparation of fluconazole monohydrate

A mixture of 2',4'-difluoro-2-(1H-1,2,4-triazol-1-yl)acetophenone (5.0g, 22.4mmol), trimethylsulfoxonium iodide (6.0g, 26.88mmol), 1,2,4-triazole (1.55g, 22.4mmol), and potassium hydroxide (3.55g, 53.76mmol) were refluxed for 1 hour in the presence of a co-solvent (40ml) consisting of potassium hydroxide solution and isopropanol dissolved in distilled water, based on the a mixing ratio of the following table 3. Then the reaction was carried out in the same manner as described in the example 1.

As a result, a white solid compound, so prepared, was confirmed to be fluconazole monohydrate, and it coincided with those materials prepared by the Korean Patent Application No. 82-2493, and U.K. Patent Application No. 2270521 (1993) in terms of IR (KBr), 1H NMR (DMSO-d6) and water content (5.6%).

Table 3.

Mixing ratio between water and isopropanol	10 : 1	2 : 1	1 : 5	1 : 10
Yield	5.4g(74.5%)	5.45g(75%)	5.15g(71%)	4.8g(66%)

Example 7: Preparation of fluconazole anhydrous

Fluconazole monohydrate (5.0g, 15.42mmol), so prepared from the example 1, was completely dissolved in a hot isopropanol (25ml), cooled again at below 5℃ and stirred for 1 hour. The precipitate, so generated, was filtered and dried under reduced pressure.

The above solid was confirmed to be fluconazole anhydrous (4.5g, yield: 95%) and it coincided with those materials prepared by the Korean Patent Application No. 82-2493, and U.K. Patent Application No. 2270521 (1993) in terms of water content (0.1% or less).

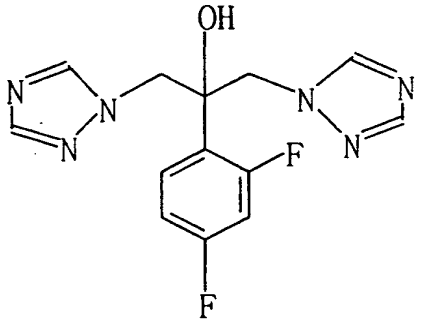
M.P.: 138℃

The process of manufacturing fluconazole according to said invention is suitable for the large-scale production of fluconazole since said reaction with respect to the final product shows an improved yield even in a short period of time (1 to 2 hours) by using a reaction solvent such as water, or an organic solvent to be mixed with water or water-mixed co-solvent, wherein all reactants are homogeneously reacted under a mild condition with easily handled reagents.

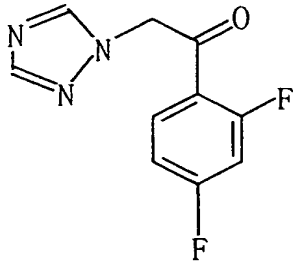
What is claimed is:

1. Process for manufacturing fluconazole of formula 1, and the pharmaceutically acceptable salt or monohydrate thereof by using the compound of formula 2 as a starting substance and compounds of formula 2, and 3, wherein said compounds of formula 3 and 4 are added to the compound of formula 2 for the one-pot reaction in the presence of a reaction solvent such as water, or a co-solvent comprising water soluble organic solvent and water.

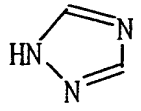
Formula 1



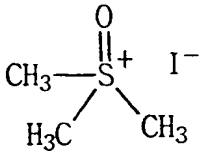
Formula 2



Formula 3



Formula 4



2. Process for manufacturing fluconazole, and the pharmaceutically acceptable salt or monohydrate thereof according to claim 1, wherein said organic solvent, which may be mixed with water, is selected from acetonitrile, dimethylformamide, dimethyl sulfoxide, and one or more lower alcohols having 1-4 carbons.

3. Process for manufacturing fluconazole, and the pharmaceutically acceptable salt or monohydrate thereof according to claim 1 or 2, wherein water and organic solvent for said co-solvent are mixed in a volume ratio of 10:1 to 1:10.

4. Process for manufacturing fluconazole, and the pharmaceutically acceptable salt or monohydrate thereof according to claim 1, wherein said reaction is carried out in the presence of a base.

5. Process for manufacturing fluconazole, and the pharmaceutically acceptable salt or monohydrate thereof according to claim 1 or 3, wherein said reaction is carried out within the range of 50℃ to the reflux temperature.

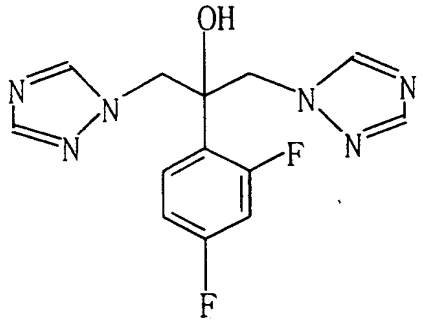
6. Process for manufacturing fluconazole, and the pharmaceutically acceptable salt or monohydrate thereof according to claim 1, wherein said fluconazole monohydrate is dissolved by alcohol solvent within the range of 40℃ to the reflux temperature, cooled below 5℃, and under precipitation or reduced pressure, said solvent is removed in order to produce fluconazole anhydrous.

AMENDED CLAIMS

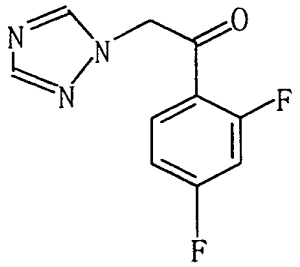
[received by the International Bureau on 9 June 1998 (09.06.98); original claim 4 cancelled; original claim 1 amended; claims 2,3,5 and 6 renumbered as claims 2-5 (2 pages)]

1. Process for manufacturing fluconazole of formula 1, and the pharmaceutically acceptable salt or monohydrate thereof by using the compound of formula 2 as a starting substance and compounds of formula 2, and 3, wherein said compounds of formula 3 and 4 are added to the compound of formula 2 for the one-pot reaction under the homogeneous condition in the presence of a base and a reaction solvent such as water, or a co-solvent comprising water soluble organic solvent and water.

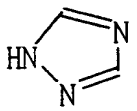
Formula 1



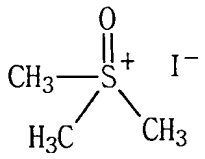
Formula 2



Formula 3



Formula 4



2. Process for manufacturing fluconazole, and the pharmaceutically acceptable salt or monohydrate thereof according to claim 1, wherein said organic solvent, which may be mixed with water, is selected from acetonitrile, dimethylformamide, dimethyl sulfoxide, and one or more lower alcohols having 1-4 carbons.

3. Process for manufacturing fluconazole, and the pharmaceutically acceptable salt or monohydrate thereof according to claim 1 or 2, wherein water and organic solvent for said co-solvent are mixed in a volume ratio of 10:1 to 1:10.

4. Process for manufacturing fluconazole, and the pharmaceutically acceptable salt or monohydrate thereof according to claim 1 or 3, wherein said reaction is carried out within the range of 50℃ to the reflux temperature.

5. Process for manufacturing fluconazole, and the pharmaceutically acceptable salt or monohydrate thereof according to claim 1, wherein said fluconazole monohydrate is dissolved by alcohol solvent within the range of 40℃ to the reflux temperature, cooled below 5℃, and under precipitation or reduced pressure, said solvent is removed in order to produce fluconazole anhydrous.

Figure 1a

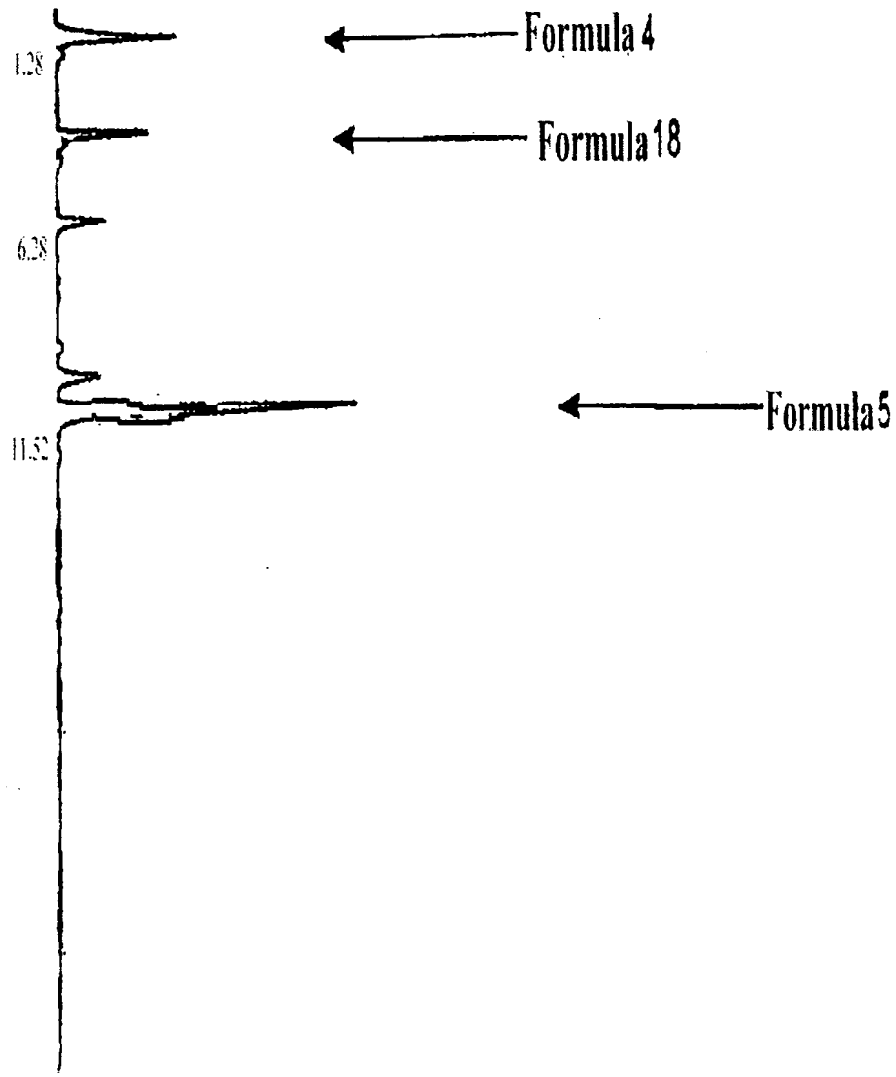


Figure 1b

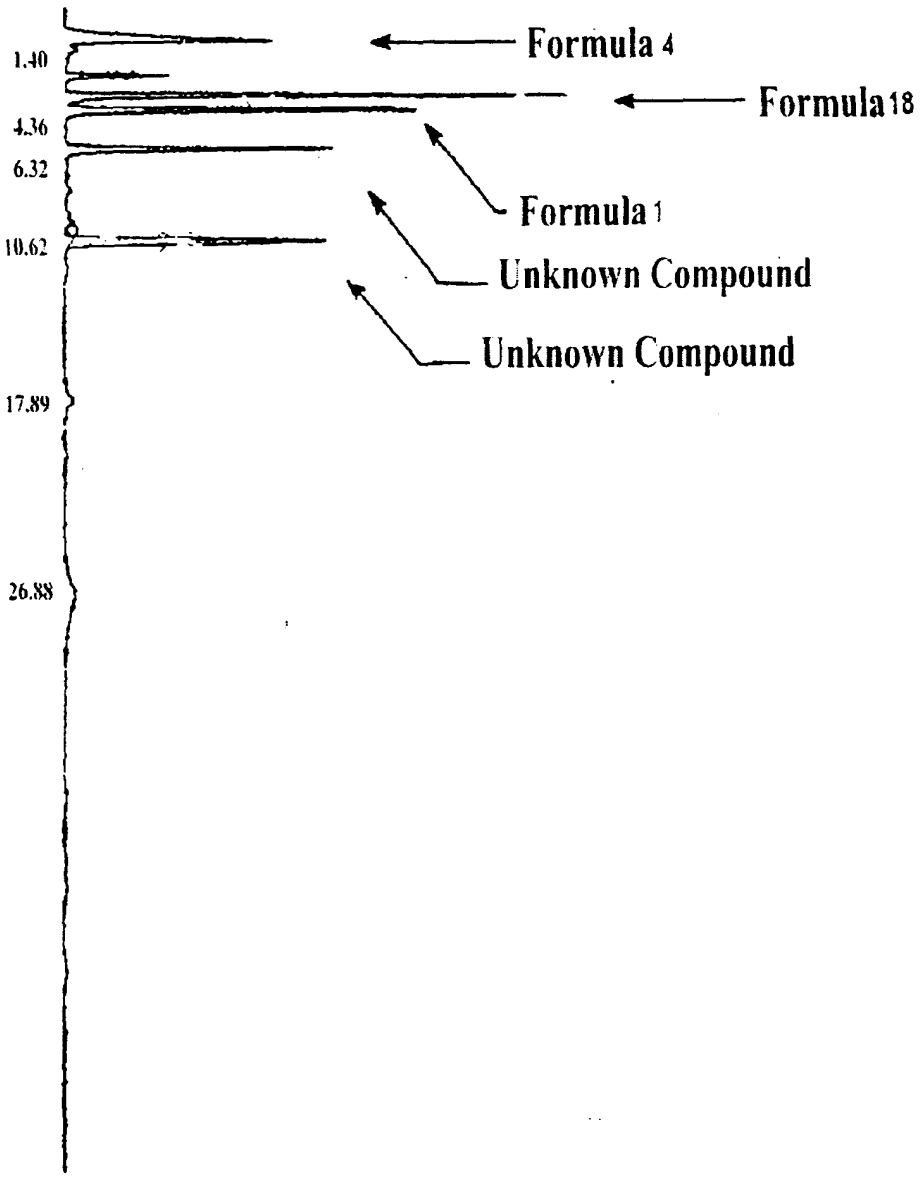

1.40
4.36
6.32
10.62
17.89
26.88
Formula 4
Formula 18
Formula 1
Unknown Compound
Unknown Compound

Figure 2

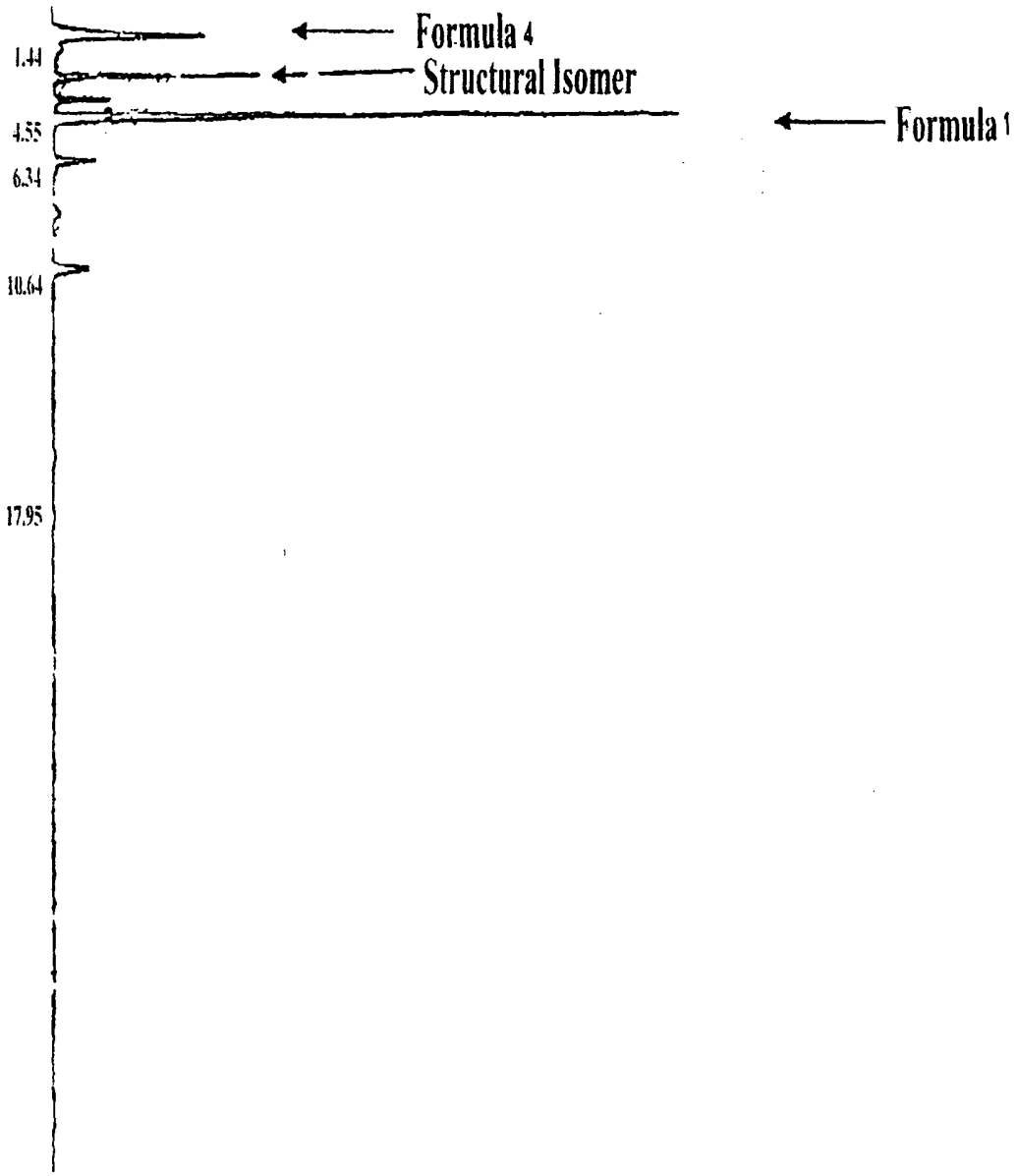
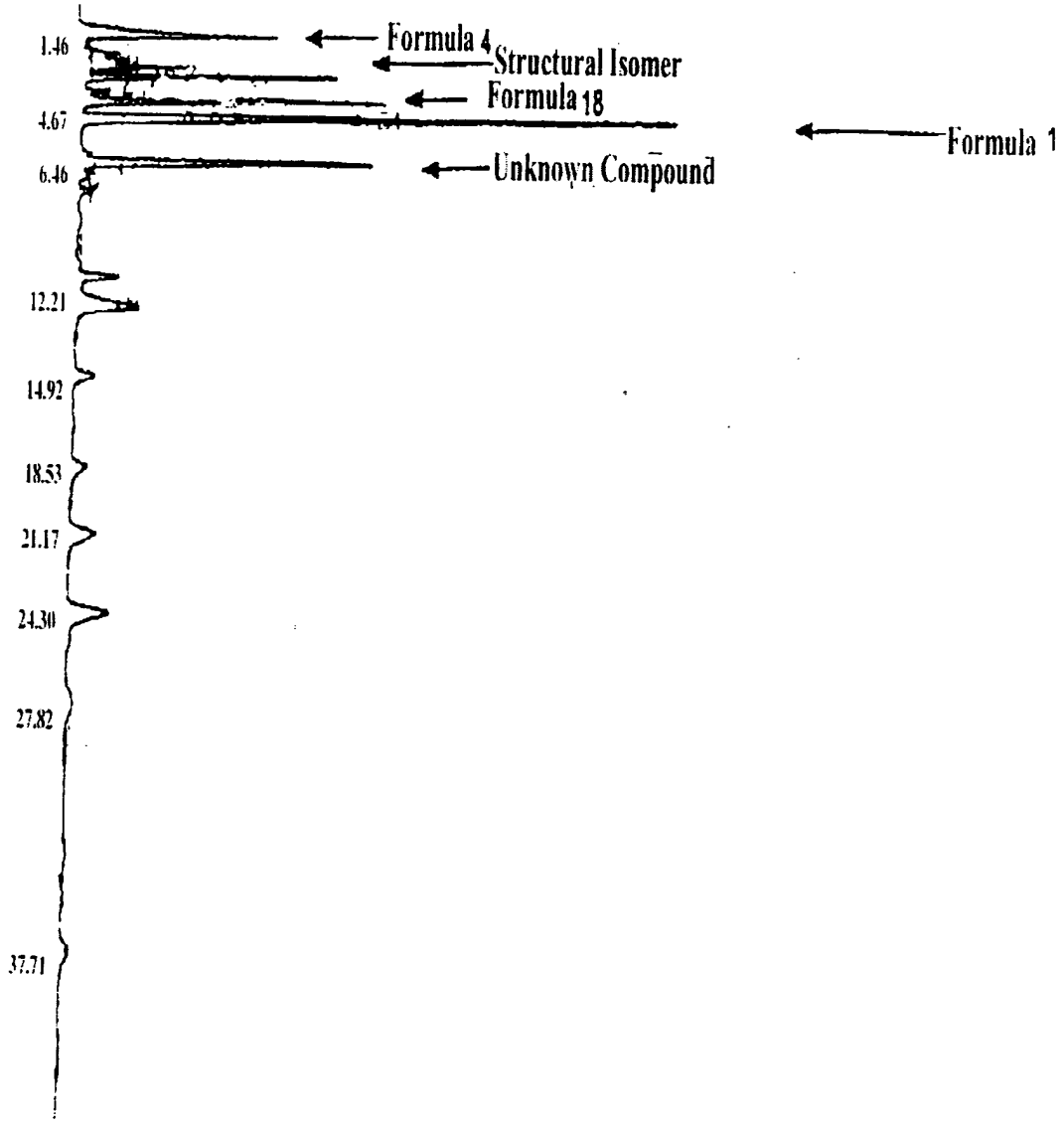


Figure 3


Formula 4
Structural Isomer
Formula 18
Formula 1
Unknown Compound
1.46
4.67
6.46
12.21
14.92
18.53
21.17
24.30
27.82
37.71

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 98/00018

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: C 07 D 249/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: C 07 D 249/08

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT, Chem. Abstr.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Questel: WPIL STN: CAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 069 442 A1 (PFIZER LTD.) 12 January 1983 (12.01.83), examples 2e,2d.	1-6
Y	Chemical Abstracts, Vol.120, No.21, 23 May 1994 (Columbus, Ohio, USA), page 1054, column 2, abstract No.270250p, NARAYANAN, A. et al.:"Conversion of 4-amino-4H-1,2,4-triazole to 1,3-bis(1H-azol-1-yl)= -2-propanols and 1-phenacyl-4-[(benzoyl or 4-toluene= sulfonyl)imino]-(1H-1,2,4-trizolium) ylides", & J. Heterocycl. Chem. 1993, 30(5), 1405-12 (Eng).	1-6
A	US 5 508 423 A (MURTHY et al.) 16 April 1996 (16.04.96), claim 1.	1
A	WO 95/07 895 A1 (ACIC INC.) 23 March 1995 (23.03.95), claim 1.	1
A	WO 96/20 181 A1 (ACIC INC.) 04 July 1996 (04.07.96), claim 1 (cited in the application).	1
A	Chemical Abstracts, Vol.106, No.9, 02 March 1987 (Columbus, Ohio, USA), page 615, column 1, abstract No.67325k, MONTSERRAT, F.E.:"Process for the	1

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
01 April 1998 (01.04.98)	15 April 1998 (15.04.98)
Name and mailing address of the ISA/ AT AUSTRIAN PATENT OFFICE Kohlmarkt 8-10 A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer Hammer Telephone No. 1/53424/374

Form PCT/ISA/210 (second sheet) (July 1992)